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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/271,584	03/18/99	BLUMWALD E	4001

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EXAMINER	
KUBELIK,A	
ART UNIT	**PAPER NUMBER**
1638	17

DATE MAILED: 04/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/271,584	BLUMWALD ET AL.	
	Examiner	Art Unit	
	Anne Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33,48,49 and 53-55* is/are pending in the application.

4a) Of the above claim(s) *15,16,33,48 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,17-32 and 53-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 1999* is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I (claims 1-14, 17-32, and 53-55 to the extent they read on SEQ ID NO:1) in Paper No. 11 is acknowledged. The traversal is on the ground(s) that because AtNHX1-4 are all Na^+/H^+ transporters from *Arabidopsis thaliana*, they, and thus the nucleic acids that encode them, are all species of a single invention. This is not found persuasive because Fig. 2b and 2c of the specification show that these proteins have different amino acid sequences; additionally, the amino acid sequence of the modified AtNHX protein differs from that of AtNHX1 after amino acid 496. Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute **independent and distinct** inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Thus, nucleotide sequences encoding different proteins are not species of a single invention, but constitute independent and patentably distinct inventions. Additionally, a search of more than one sequence represents a severe burden on PTO resources.

The requirement is still deemed proper and is therefore made FINAL.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement for Groups VI and VII, the restriction of these groups has been treated as though it were without traverse (MPEP § 818.03(a)).

Drawings

2. The drawings are objected to for the reasons indicated on accompanying form PTO 948. Correction is required.

Claim Objections

3. Claims 19, 21, 26 and 31 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). For the purposes of examination, claims 19 and 21 were treated as though they were only dependent on claim 8, claim 26 was treated as though it were only dependent on claim 17, and claim 31 as though it were dependent only on claim 21. Such treatment does not relieve Applicant of the responsibility to respond to this objection.

4. Claims 2-6, 8-14, 17-32 and 55 are objected to because they contain nonelected matter. Dependent claims are included in the objection.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-14 and 17-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids that encode SEQ ID NO:2, does not reasonably provide enablement for nucleic acids with homology to those nucleic acids or encode fragments of a transporter. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a multitude of nucleic acids that hybridize to nucleic acids that encode SEQ ID NO:2, that have at least 17% homology to SEQ ID NO:1, or that comprise a part or fragment of those nucleic acids. The instant specification, however, fails to provide guidance for which amino acids can be altered, deleted or added to make those make those nucleic acids and which portions of the gene should be deleted to make the fragments or parts.

It cannot be predicted by one of skill in the art that a nucleic acid that hybridizes to nucleic acids that encode SEQ ID NO:2, that has 17% homology to SEQ ID NO:1, or that encodes a part of any size of SEQ ID NO:2 will encode a transporter. Bowie et al (1990, Science 257:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into unique three-dimensional structures that allows it to function and carry out the instructions of the genome. Bowie et al teach that while many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or none at all (pg 1306, right column). The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252), who teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect, but that a replacement

with serine or glutamic acid sharply reduced biological activity (see the abstract). Small changes in amino acid sequence can completely modify enzymatic function; Broun et al (1998, Science 282:1315-1317) teach that a change of four amino acids converts an oleate 12-desaturase to a hydroxylase. Thus, Lazar et al and Broun et al demonstrated that one or few amino acid substitutions could dramatically affect the biological activity and the structure-function characteristics of a protein.

In addition, Bork (2000, Genome Res. 10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (pg 398, column 1). One of the reasons for this inaccuracy is that protein function is context dependent, and both molecular and cellular aspects must be considered (pg 398, column 2). Conclusions from comparison analyses are often stretched with regard to protein products (pg 398, column 3). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply certain functionality (see pg 399, Table 1 legend). Bork cautions that, although current methods seem to capture important features and define general trends, 30% of structure-function features are missing or predicted inaccurately. This must be kept in mind when processing the results (pg 400, paragraph spanning columns 1 and 2). Thus, given the teachings of Bowie et al, Lazar et al, and Broun et al, and given the limitations and pitfalls of using computational sequence analysis, as taught by Bork, it is apparent that the biological function of a protein encoded by a nucleic acid

with 17% sequence similarity to AtNHX1 or that hybridizes to part of SEQ ID NO:1 cannot accurately be predicted.

The above can be illustrated with the following example: a nucleic acid of SEQ ID NO:1 would hybridize to a nucleic acid that encodes a urea transporter protein (Hediger et al, 19995, US Patent 5441875; see sequence search results).

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acid with 17% sequence similarity to AtNHX1 or that hybridizes to part of SEQ ID NO:1.

7. Claims 1-14, 17-32 and 53-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a multitude of DNA molecules that have 17% sequence similarity to SEQ ID NO:1 due to the deletion, insertion or substitution of an unspecified number of nucleotides that hybridize to any nucleic acid encoding SEQ ID NO:2, that encode fragments of any length of SEQ ID NO:2, or that encode a Na^+/H^+ transporter from any source. In contrast, the specification only provides guidance for a coding sequence from *Arabidopsis* that comprises SEQ ID NO:1 or that encodes the entire SEQ ID NO:2. No guidance is presented for the alteration of any part of SEQ ID NO:1 to any degree, or for the identification of any other sequence from any other plant species, and no guidance is presented regarding the evaluation of these sequences in transgenic plants.

Given the claim breadth and lack of guidance as discussed above, the specification fails to provide an adequate written description of the claimed invention.

See *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism that would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

See Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ 2d 1016 at 1021 and 1027, (Fed. Cir. 1991) at page 1021, where it is taught that a gene is not reduced to practice until the inventor can define it by "its physical or chemical properties" (*e.g.*, a DNA sequence), and at page 1027, where it is taught that the disclosure of a few gene sequences did not enable claims broadly drawn to any analog thereof.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-14, 17-32 and 53-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

Claims 1-2, 4-5, 7, 12, 26 and 53 are indefinite in their recitation of the phrase "capable of increasing." For example, in claim 53, the use of the phrase "capable of increasing" suggests that while the transporter can increase salt tolerance, it is not necessary for the invention that it does so. In claim 53, this rejection can be obviated by replacing "capable of increasing" with --

that increases-- and "capable of providing" with --that provides--. Similar modifications can be made to the other claims. Dependent claims are included in the rejection.

Claims 28-29 are indefinite in their recitation of the word "includes" or "include." It is unclear if this word is intended to be open or closed. If open language is intended, the word should be replaced with --comprises--.

Claim 3 is indefinite in its recitation of "conditions about those in Table 4." The conditions should be listed in the claim.

Claim 23 is indefinite in its recitation of "the plants in Table 5." The plants should be listed in the claim.

Claims 28-29 recite the limitation "the host cell." There is insufficient antecedent basis for this limitation in the claims.

Claim 2, part b, is indefinite in its recitation of "wherein the nucleic molecule." For purposes of examination, it was assumed that "acid" should have been present after "nucleic." Such treatment does not relieve Applicant of the responsibility to respond to this rejection. Dependent claims are included in the rejection.

The term "enhances" in claim 8 is a relative term that renders the claim indefinite. The term "enhances" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The extent to which transcription is altered is unclear.

The term "elevated" in claim 32 is a relative term that renders the claim indefinite. The term "elevated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably

apprised of the scope of the invention. The extent to which the levels of the protein is increased is unclear.

The term "increased" in claims 12 and 53 is a relative term that renders the claims indefinite. The term "increased" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The extent to which salt tolerance is increased is unclear.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claims 1-14, 17, 19-20 and 26 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Brant et al (1997, GenBank Accession No. T51330).

Brant et al teach a nucleic acid that encodes a human Na^+/H^+ transporter, that would have at least 17% homology to SEQ ID NO:1, that comprises part of SEQ ID NO:1, and that would increase salt tolerance in a cell (see sequence search results). For the purpose of sequencing, this nucleic acid would be contained in a vector like pUC18 or pBluescript, which have promoters,

and transformed into *E. coli*. It would also comprise a fragment of an AtNHX nucleic acid, and would be the same regardless of source.

12. Claims 1-14, 17, 19-20 and 26 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sumitomo Sieyaku KK (1993, GenBank Accession No. Q51524).

Sumitomo Sieyaku KK teach a nucleic acid that encodes a rabbit Na^+/H^+ transporter, that would have at least 17% homology to SEQ ID NO:1, that comprises part of SEQ ID NO:1, and that would increase salt tolerance in a cell (see sequence search results). For the purpose of sequencing, this nucleic acid would be contained in a vector like pUC18 or pBluescript, which have promoters, and transformed into *E. coli*. It would also comprise a fragment of an AtNHX nucleic acid, and would be the same regardless of source.

13. Claims 1-14, 17, 19-20 and 26 are rejected under 35 U.S.C. 102(a) as being anticipated by Dante et al (1997, GenBank Accession No. AF007271).

Dante et al teach a genomic clone that encodes the protein of SEQ ID NO:2 (see sequence search results). For purposes of sequencing, this nucleic acid would be contained in a vector with promoters and a bacterial cell.

14. Claims 1-14, 17-20, 26 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Hahnenberger et al (1996, Proc. Natl. Acad. Sci., USA 93:5031-5036).

Hahnenberger et al teach the Na^+/H^+ transporter *sod2*, which would hybridize to SEQ ID NO:1 or would also comprise a fragment of an AtNHX nucleic acid, and its transformation into yeast (pg 5033, left column, paragraph 3, to pg 5034, right column, paragraph 1), and vectors comprising the DNA with the 35S promoter (pg 5031, right column, last paragraph).

15. Claims 1-14, 17-24, 26-32 and 53-54 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Young et al (WO 91/06651).

Young et al teach tobacco and *Arabidopsis* plants transformed with a gene encoding the Na^+/H^+ transporter *sod2*, which would hybridize to SEQ ID NO:1 or would also comprise a fragment of an AtNHX nucleic acid, and the resistance of these transgenic plants to LiCl (pg 28, paragraph 3, to pg 35). Young et al also teach that that these plants would be resistant to high sodium concentration (pg 9, paragraph 1). The *sod2* gene encodes a THX transporter, which the instant specification defines as a Na^+/H^+ transporter that is capable of increasing salt tolerance in a cell (pg 20, lines 23-24).

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-14, 17-32 and 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young et al (WO 91/06651) in view of Gordon-Kamm et al (1990, Plant Cell 2:603-618).

The claims are drawn to plants, including monocots, transformed with a nucleic acid that encodes a Na^+/H^+ transporter that hybridizes to SEQ ID NO:1, comprises a fragment of an AtNHX nucleic acid, or confers salt tolerance, nucleic acids that encode those Na^+/H^+ transporters, and methods for production of those plants.

Young et al teach tobacco and *Arabidopsis* plants transformed with a gene encoding the Na^+/H^+ transporter *sod2* (pg 28, paragraph 3, to pg 35), as discussed above. Young et al do not disclose monocots transformed with that gene.

Gordon-Kamm et al teach transformation and regeneration of maize.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to transform the *sod2* gene into plants as taught by Young et al, and to modify that to transform it into a monocot as described in Gordon-Kamm et al. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Young et al to do so (pg 9, paragraph 1).

18. Claim 55 is free of the prior art, given the failure of the prior art to teach or suggest the isolated nucleic acid of SEQ ID NO:1.

Conclusion

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached on Monday - Friday, 8:15 am-4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne R. Kubelik, Ph.D.
April 5, 2001

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638